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| EXAMINER | |
|---|---|
| YAO, LEI | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/663,431 | MORRIS ET AL. | |
| | Examiner | Art Unit | |
| | LEI YAO | 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *74,76-78,90,93 and 94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *74, 76-78, 90, 93, and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

***Response to Amendment and Arguments***

The Amendment filed on 9/30/2008 in response to the previous Non-Final Office Action (4/1/2008) is acknowledged and has been entered.

Claims 1-73, 75, 79-89, 91-92, and 95-97 are cancelled.

Claims 74, 76-78, 90, 93, and 94 are pending and under consideration for a method of diagnosing a cancer to the extent of breast cancer (elected) comprising determining the levels of expression of VLDLR mRNA of SEQ ID NO: 43.

The following office action contains NEW GROUNDS of rejection-based on the amendment.

***Information Disclosure Statement***

The information disclosure statement (s) (IDS) submitted on 10/1/2008 are/is considered by the examiner and initialed copies/copy of the PTO-1449 are/is enclosed.

***Rejections/Objections Withdrawn***

The objection of the specification because of containing embedded hyperlink is withdrawn in view of amendment by deleting embedded hyperlink.

The rejection of claims 61, 74-81, 84, 86-89 and 94-97 under 35 U.S.C. 102(a) or 102(e) as being anticipated by Hopkins et al is withdrawn in view of cancellation of claims, amendment to the claims, and Applicant's argument.

***Rejection Maintained and Response to Arguments***

***Oath/Declaration:***

The copy of the declaration filed with this response (9/30/2008) is still defective because of missing signature of inventor David W. Morris. Two inventors are listed in the declaration of this application and only inventor Marc Malandro signed the declaration filed on November 15, 2004. The new declaration submitted on 9/30/2008 is an identical copy as one recorded in the PTO database. A new oath or declaration including a signature of inventor David W. Morris is required to comply with 37 CFR 1.67(a) identifying this application by application number and filing date.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the **first paragraph** of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

*Written Description*- Method comprising detecting a variant of SEQ ID NO: 43

Claims 74, 76, 78, 90, 93 and 94 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant states that the independent claims 74 and 90 have been amended and have written description sufficient to satisfy the MPEP and the Written Description Guidelines (bridging page 8-9). In response, claims 74 and 90 are amended to incorporate the limitation of certain cancelled claims, however, the scope of claimed invention is not changed, which is still drawn to a method of detecting a variant of SEQ ID NO:43 having 98% or 95% more sequence identity or by hybridizing. Neither the specification nor the state of the art has described such variant. The amended claims also recite detecting a complement of the mRNA of SEQ ID NO: 43. It is well known that the cellular mRNA transcript expressed in a mammalian cell is single strand nucleotides that encodes a biologically functional protein (the Office would like to provide a reference if Applicant requires). The complement of SEQ ID NO: 43 (mRNA) contains total different nuclei acids from the mRNA self in the sequences and encodes a different protein that would have totally differently biological function. Neither the specification nor the state of the art has described a nucleotides that is a complement of the mRNA of VLDLR (SEQ ID NO: 43) and is detected at an increased level in a breast cancer cell. Therefore, Applicant does not show having a possession of a full or part complement of VLDLR mRNA (SEQ ID NO: 43) and a method of using the complement.

Applicant further argues that the nucleic acids of SEQ ID NO: 43 is a representative of a genus of variants having more than 95% sequence identity to the sequence of SEQ ID NO: 43 (page 9, last para). At page 10, Applicant refers the Written Description Training Materials (2008), example 11A claiming 85% sequence

identity without function X (claim 1) or with function X (claim 2). The training material thesuggests that claim 1 without function X will not be rejected under written description. However the claim 2 reciting 85% sequence identity to SEQ ID NO: 2 with function X does not satisfy the written description requirement because one of skill in the art would not accept the disclosure of SEQ ID NO: 2 as a representative of other proteins having function X. Similarly, the instant claims would be rejected for the same reason because the mRNA of SEQ ID NO: 43 would not represent other variants of this mRNA having the claimed function of increased expression in the breast cancer cells. Regarding claim 90, at last paragraph of page 10, Applicant cites example 6 of the Written Description Training Materials and argues that under the highly stringent condition, nucleic acids that hybridize to the recited sequence must share many nucleotides in common with the recited sequence. In response, claim 3 of example 6 reciting a genus of isolated nucleic acids under highly stringent conditions hybridizing a nucleic acid encoding a protein that binds to the NDG receptor and stimulates tyrosine kinase activity. According to the training material, the claim 3 failed to satisfy the written description requirement because without a recognized correlation between structure and function those of ordinary skill in the art would not be able to identify which of those nucleic acids that hybridizes to SEQ ID NO: 43 is actually overexpressed in the breast cancer cells and be used for diagnosing the breast cancer. Thus, those of ordinary skill in the art would not consider the Applicant having been in possession of the claimed genus of nucleic acids based on the single species disclosed.

Applicant finally argue that the silence of the cited reference with respect to variants of VLDLR fails to indicate that the present specification lacks written description, rather the specification provides sufficient written description for claimed invention. In response, the Written Description Training Materials (2008, page 7) has set up a standard for determination of whether the Applicant was in possession of the claimed invention that comprises:

a……..

e. levels of skill and knowledge in the art.

f. predictability in the art.

Thus, there is no knowledge in the art that has described a variant of VLDLR mRNA identified in a breast cancer cell or tissue and no description of the instant specification is provided as discussed above. The skill in the art would not predict a role of a variant of VLDLR in the breast cancer cells and would conclude that the Applicant was NOT in possession of the claimed invention.

*Scope of Enablement*

Claims 74, 76, 78, 90, 93 and 94 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for diagnosing beast caner comprising determining and comparing the levels of the nucleotide sequence of SEQ ID NO: 43 and a method of detecting one variant of VLDLR disclosed in the art (see art rejection below), does not reasonably provide enablement for the method of detecting a cancer comprising breast cancer by determining and comparing

the levels of a variant of VLDLR or any nucleotides having at least 95% or 98% sequence identity to SEQ ID NO: 43.

Applicant states that independent claims 74 and 90 have been amended, the specification indicates that SEQ ID NO: 43 is cancer associated sequence. One skill in the art can be readily determined if expression of a nucleic acid having the nucleotide sequence more than 95% identity to SEQ ID NO: 43 based on the hybridization taught in the specification. In response, the Office agrees with Applicant on that a variant having more than 95% sequence identity to SEQ ID NO: 43 could be picked up by hybridization. However, the skilled artisan would ask "are those variants overexpressed in the breast cancer cells? Could the expression of those variants be used for diagnosing a breast cancer? One skill in the art clearly knows that a variant comprising one or more point mutations, deletions, or substitutions of a gene could totally destroy the function of the encoded protein. Are these variants or mutants still having an ability to bind to lipoprotein in the normal or cancerous cells or functionally involved in the cancer development? The instant specification does not provide any variant of SEQ ID NO: 43 up to 95% sequence identity being expressed at a higher level of a test breast cancer or any caner cell, which could lead to possible use for diagnosing a breast cancer. Based on the teaching of the art, skill in the art would not predict using any variant of SEQ ID NO: 43 in the claimed method since no variant has been identified in the art. Thus. one skilled in the art would and could not practice claimed method of detecting any variant picked by hybridization for diagnosing breast cancer.

***The following is a New Ground of rejection-based on the amendment***

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

It is noted that based on the current amendment the following rejection is reformed with the same reference and evidence.

Claims 74, 76-78, 93, and 94 remain and are rejected again under 35 U.S.C. 102(b) as being anticipated by Martensen et al., (Eur. J. Biochem. vol 248, page 583-591, 1997) as evidenced by sequence search results.

Claims are drawn to a method for diagnosing caner comprising determining and comparing the levels of an expression product comprising a nucleotide sequence of very low density lipoprotein receptor (VLDLR) mRNA or a gene product having at least 95% or 98% sequence identity to or comprising a nucleotide sequence of SEQ ID NO: 43, complement or the homologous identified by hybridization in the breast cancer patient samples to the normal control samples, wherein the VLDLR binds to LDL, and diagnosing a breast cancer based on at least 50% an increase expression of VLDLR compared to the normal tissues or control indicates breast cancer.

Martensen et al., disclose a method which could be used for diagnosing a breast cancer by determining the levels of expression of VLDLR. Martensen et al., first disclose two human VLDLR variants VLDLR-I and VLDLR-II and disclose that difference between two receptors is lack of 84 nucleotides that encodes the domain with potential

O-linked glycosylation (exon 16) of VLDLR-II (page 584, col 1). Martensen et al., cite a reference of Webb et al., (page 584, col 1, para 1, and page 591, col 2, reference No.9), who disclose the sequence of VLDLR, which is encoded by the SEQ ID NO: 43 of instant claims as evidenced by the sequence search result (attached, page 1, Webb et al., highlight). The cDNA, or mRNA of SEQ ID NO: 43 of the claims encodes the second VLDLR-II without exon 16 as evidenced by the sequence search result. Martensen et al., further disclose binding VLDLRs to its ligand, lipoprotein (page 583, col 1 and page 588, col 1).

Martensen et al., disclose method steps of determining a breast cancer comprising comparing the levels of expression of gene product in breast cell lines and carcinoma tissue samples to the normal cells or tissues (figure 1 and 5, page 585-6). Martensen et al., point out that the human breast carcinoma expresses predominantly or exclusively the variant lacking exon 16 (VLDLR-II, abstract, figure 5). Martensen et al., compare the gene expression pattern from the cell line isolated from breast cancer tissues to the normal cells and display the expression levels (figure 5) that is more than 50%, 100%, or more increased.

Since claimed method is not drawn to a specific oligonucleotide as primers or a probe for the hybridization or RT-PCR, the method of Martensen et al., would detect the nucleotide sequence having at least 95% identity to the sequence of SEQ ID NO: 43 or its full or part complement (page 586, col 2) and would anticipate the claimed method.

Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection above.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquires set forth in Graham V. john Deere Co., 383 U.S. 1, 148 USPQ 459 (1996), that are applied for establishing a background for determining obviousness under 25 U.S. 103 (a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

It is noted that based on the current amendment the following rejection is reformed with the same references.

Claim 90 remains and is rejected again under 35 U.S.C. 103(a) as being unpatentable over by Martensen et al., (Eur. J. Biochem. vol 248, page 583-591, 1997) in view of Hopkins et al., (US Application Publication, 2002/0137077, filing 10/25/2001) and Fodor et al., (US Patent No.5871928, issued 1999).

The claims are drawn to a method of diagnosing a breast cancer by contacting a polynucleotide that hybridizes under stringent condition to a nucleotide from a sample of breast cancer, wherein the hybridization is at 60°C or 56°C and 5XSSC.

The teaching of Martensen et al., is set forth above.

Martensen et al., do not teach hybridization performing at 50-60 degree and 5XSSC.

Hopkins et al., teach method of hybridization comprising contacting a polynucleotide under stringent hybridization condition at 60 ºC in 5XSSC [0064].

Fodor et al., teach that nucleotide hybridization would often be used, at about 45 ºC or even high as about 50 ºC or 60 ºC (bridging col 49-50).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the teachings to optimize the hybridization condition and determine the expression of nucleotide sequence of SEQ ID NO: 43 or its variants in the samples from breast cancer cells or tissues. One of ordinary skill in the art at the time the invention was made would have been motivated to apply the method of Hopkins et al., to the teaching of Martensen et al., in order to benefit the breast cancer diagnosis because Martensen et al., teach an increased expression of VLDLR-II in the breast cancer cell and tissues. One of ordinary skill in the art at the time the invention was made would have been further motivated to apply the teaching of Fodor et al., on using the high stringent hybridization condition at 50 ºC or 60 ºC to the method of Hopkins et al., and Martensen et al in order to screen the expression of the homologous of the gene product, SEQ ID NO: 43, because Fodor et al., suggest that the specific hybridization condition will be selected to correspond to a discriminatory condition (col 50, line 47+). One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for combining

the teachings to determine the levels of gene product of SEQ ID NO: 43 or its homologous or variants at different hybridization condition because the references in combination have shown a method for detecting the gene product in breast cancer and the hybridization could be at 50ºC or even higher. Therefore, the references in combination teach each and every limitation of the claims and the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results.

Applicant's arguments have been considered but are moot in view of the new ground(s) of rejection above

***Conclusion***

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

## *Conclusion*

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-6.00pm Monday-Thursday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Lei Yao, Ph.D./
Examiner, Art Unit 1642

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643